Registry No.—**3**, 30345-08-5; **4**, 30345-09-6; **5**, 30345-10-9.

Acknowledgment.—The authors wish to thank the Public Health Service for financial support of this work under Grant No. CA-04536-13 from the National Cancer Institute.

A Novel Synthesis of β-Keto Sulfides

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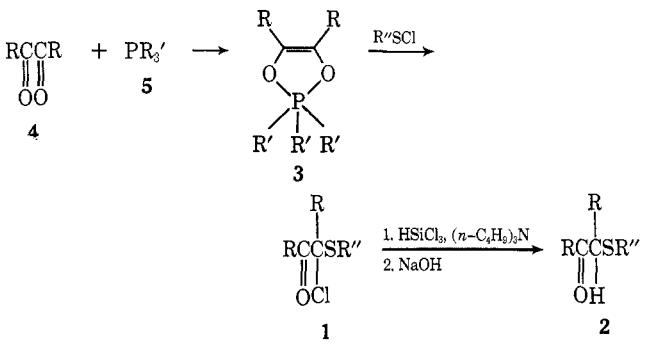
Received December 31, 1970

The general utility of β-keto sulfides (and their corresponding sulfoxide derivatives) is well documented.[2] These sulfides are most commonly prepared by the action of mercaptides (RS^-) on α-halo ketones,[3a] by reacting sulfenyl halides with ketones[2a] and by the decomposition of dialkylphenacylsulfonium salts with base.[3b] In addition, a number of 3-thianones have recently been prepared *via* a novel intramolecular cyclization reaction.[3c] None of the methods is widely versatile, however, since yields are often low and isomeric products and/or intermediates are encountered. We wish to report a useful new synthesis of β-keto sulfides from simple starting materials. The reactions employed proceed cleanly and in high yield.

The trichlorosilane–tri-*n*-butylamine system[4] reduces α-chloro-β-keto sulfides[5] **1** to β-keto sulfides **2** in nearly quantitative yield. The chloro keto sulfides **1** are



easily prepared[5] by the action of sulfenyl chlorides on substituted 1,3,2-dioxaphospholenes **3**. In addition, the reduction of chloro keto sulfides **1** may be carried out *in situ* from α-diketones **4** and trimethyl phosphite **5** in overall yields of 60–80%. The results are summarized in Table I.

TABLE I

No.	R	R″	Mp or bp (mm), °C	Yield, % from **1** (from **4** + **5**)	Nmr data, τ	Calcd, % C	Calcd, % H	Calcd, % S	Found, % C	Found, % H	Found, % S
2a	C_6H_5	C_6H_4-*p*-CH_3	94–96	98 (80)	1.80–3.10 (14 H, m), 4.12 (H, s), 7.73 (3 H, s)	79.21	5.70	10.07	79.16	5.72	9.98
2b	C_6H_5	$CH_2C_6H_5$	70–72	(60)	2.10–2.80 (15 H, m), 4.62 (H, s), 6.33 (2 H, AB, J = 14 Hz)	79.21	5.70	10.07	79.02	5.75	9.97
2c	C_6H_5	CH_2CH_3	78–80	(62)	1.80–2.90 (10 H, m), 4.37 (H, s), 7.50 (2 H, split AB, J = 7 Hz), 8.83 (3 H, t, J = 7 Hz)	74.96	6.29	12.51	74.85	6.33	12.43
2d	CH_3	C_6H_5	78–80 (0.003)	80 (61)	2.30–2.85 (5 H, m), 6.29 (H, q, J = 7 Hz), 7.80 (3 H, s), 8.63 (3 H, d, J = 7 Hz)			17.79			17.85
2e	CH_3	CH_2CH_3	Dec								

Experimental Section

Reaction of α-Benzoyl-α-chlorobenzyl *p*-Tolyl Sulfide (1a) with Trichlorosilane and Tri-*n*-butylamine.—In a 50-ml flask, fitted with a condenser carrying a drying tube and a dropping funnel, was dissolved α-benzoyl-α-chlorobenzyl *p*-tolyl sulfide (1) (0.70 g, 0.02 mol) in dry dimethoxyethane (10 ml). Tri-*n*-butylamine (0.37 g, 0.02 mol) was added, followed by trichlorosilane (0.36 g, 0.026 mol). The reaction mixture was refluxed for 2–3 hr. At the end of the reflux period, it was cooled and poured into a cold solution of 2 *N* sodium hydroxide[6] with stirring. The sodium hydroxide solution was extracted with several portions of methylene chloride. The methylene chloride extracts were combined and washed successively with water, dilute acid, and then water, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residual solid recrystal-

(1) NRCC scholarship recipient, 1967–1970.

(2) (a) C. Rappe, "Mechanisms of Reactions of Sulfur Compounds," Vol. 4, IntraScience Research Foundation, 1969, p 95. (b) M. C. Caserio, W. Lauer, and T. Novinson, *J. Amer. Chem. Soc.*, **92**, 6082 (1970); G. A. Russell and G. Hamprecht, *J. Org. Chem.*, **35**, 3007 (1970), and references cited therein; G. A. Russell and E. T. Sabourine, *ibid.*, **34**, 2336 (1969).

(3) (a) T. C. Whitner and E. E. Reid, *J. Amer. Chem. Soc.*, **43**, 638 (1921); L. M. Long, *ibid.*, **68**, 2159 (1946). (b) H. Böhme and W. Krause, *Chem. Ber.*, **82**, 426 (1949). (c) P. T. Lansbury, E. J. Nienhouse, D. J. Scharf, and F. R. Hilfiker, *J. Amer. Chem. Soc.*, **92**, 5649 (1970).

(4) These reagents have been used to reduce a number of functionalities: see T. H. Chan, J. P. Montillier, W. F. Van Horn, and D. N. Harpp, *ibid.*, **92**, 7224 (1970); R. A. Benkeser, K. M. Foley, J. M. Gaul, and G. S. Li, *ibid.*, **92**, 3232 (1970); R. A. Benkeser and W. E. Smith, *ibid.*, **90**, 5307 (1968).

(5) D. N. Harpp and P. Mathiaparanam, *Tetrahedron Lett.*, 2089 (1970). In addition, α-chloro-β-keto sulfides of the type RCO(R′)C(Cl)SR″ have been prepared; see F. Weygand, H. J. Bestmann, and H. Fritzsche, *Chem. Ber.*, **93**, 2340 (1960), and references cited therein.

(6) Alkaline conditions were maintained during work-up in order to eliminate any side reactions arising from the hydrolysis of the following possible intermediate, $RC(OSiCl_3)=CR(SR'')$. The trichlorosilyl anion may well be involved; see R. A. Benkeser, K. M. Foley, J. B. Grutzner, and W. E. Smith, *J. Amer. Chem. Soc.*, **92**, 697 (1970), and S. C. Bernstein, *ibid.*, **92**, 699 (1970). At present, however, it is uncertain as to the exact mechanism of this reaction.

lized from 95% ethanol, affording 0.62 g (98%), mp 91–93°. See Table I for analytical and spectral data.

Reaction of α-Benzoyl-α-chlorobenzyl Benzyl Sulfide (1b) (Prepared *in Situ*) with Trichlorosilane and Tri-*n*-butylamine.—The 1:1 benzil–trimethylphosphite adduct **3** was generated as previously described[7] from benzil (2.10 g, 0.01 mol) and trimethyl phosphite (1.25 g, 0.01 mol). Dry 1,2-dimethoxyethane (10 ml) was added, followed by sulfenyl chloride (0.01 mol) in the same solvent (10 ml). The pale yellow solution was stirred for 15 min. Tri-*n*-butylamine (1.85 g, 0.01 mol) and trichlorosilane (1.80 g, 0.013 mol) were added. The reaction mixture was worked up as in the previous experiment. The product crystallized from 95% ethanol (60%). In a similar manner sulfide **2c** was prepared in 62% yield.

Reaction of α-Acetyl-α-chloroethyl Phenyl Sulfide (1d) with Trichlorosilane and Tri-*n*-butylamine.—As described above, α-acetyl-α-chloroethyl phenyl sulfide (**1d**) (1.20 g, 0.0056 mol) was dissolved in 1,2-dimethoxyethane (10 ml). Tri-*n*-butylamine (1.10 g, 0.006 mol) and trichlorosilane (1.40 g, 0.01 mol) were added and the reaction mixture was refluxed overnight with stirring. Work-up as in the preparation of **2a** from **1a** gave sulfide **2d**: bp 78–80° (0.003 mm); yield 0.80 g (80%); ir 1720 cm^{-1} (CO). Exact mass data: calculated for $C_{16}H_{12}OS$, 180.0609; found, 180.0608.

Attempted Reaction of α-Acetyl-α-chloroethyl Ethyl Sulfide (1e) with Trichlorosilane and Tri-*n*-butylamine.—The procedure described in the previous experiment was repeated with α-acetyl-α-chloroethyl ethyl sulfide (**1e**) (1.66 g, 0.01 mol), trichlorosilane (1.80 g, 0.013 mol), and tri-*n*-butylamine (1.85 g, 0.01 mol). A black tarry mass was obtained and yielded no identifiable products.

Reaction of α-Acetyl-α-chloroethyl Phenyl Sulfide (1d) (Prepared *in Situ*) with Trichlorosilane and Tri-*n*-butylamine.—Benzenesulfenyl chloride (1.45 g, 0.01 mol) was added to a solution of 1:1 biacetyl–trimethyl phosphite adduct **3** (2.10 g, 0.01 mol) in 1,2-dimethoxyethane (10 ml) under nitrogen. Once the exothermic reaction had subsided, trichlorosilane (1.80 g, 0.013 mol) and tri-*n*-butylamine (1.85 g, 0.01 mol) were added and the reaction mixture was refluxed overnight. Usual work-up provided an oil which was chromatographed on Florisil using methylene chloride. Pure α-acetylethyl phenyl sulfide was obtained, yield 1.10 g (61%). Spectroscopic data were identical with the data of the previous sample. When ethanesulfenyl chloride was used instead of benzenesulfenyl chloride in the above procedure, only an intractable tarry oil was obtained.

Registry No.—**2a**, 17527-58-1; **2b**, 23343-23-9; **2c**, 16222-12-1; **2d**, 13023-53-5; **2e**, 19170-22-0.

Acknowledgment.—We wish to thank the Defence Research Board of Canada (Grant No. 9530-97) and the Research Corporation for financial support of this work.

(7) P. Mathiaparanam, Ph.D. Thesis, McGill University, Dec 1970; F. Ramirez and N. B. Desai, *J. Amer. Chem. Soc.*, **85**, 3252 (1963), and references cited therein.

Alkylation of Pyridine with *tert*-Butyllithium. Convenient Syntheses of 2,6-Di-*tert*-butylpyridine and 2,4,6-Tri-*tert*-butylpyridine

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Received January 21, 1971

A large number of sterically hindered organic bases have been reported.[1] Perhaps most notable among these is 2,6-di-*tert*-butylpyridine (**1**), since it is the only base demonstrated as having the ability to distinguish between Brønsted (protonic) and Lewis acids.[2] We required pure **1** in decigram quantities for the purpose of utilizing this unique property in another investigation. An earlier report[2] of its synthesis described a multistep procedure beginning with 2-ethylpyridine and requiring purification after each step. However, it was suggested in that article that a more direct route from pyridine was feasible. A two-stage method was later employed in the synthesis of 2,6-di-*tert*-butyl-4-alkoxypyridines from 4-alkoxypyridines.[3]

Accordingly, we attempted the most straightforward route, namely, the direct alkylation of pyridine with excess *tert*-butyllithium. This approach met with success, for in one step we could obtain not only **1** in yields up to 30% but also 2,4,6-tri-*tert*-butylpyridine (**2**),[4] both compounds being isolated in the quantities we required. Under proper conditions, **2** was the predominant product (up to 55% yield). Also produced were smaller quantities of the new compound, 2,4-di-*tert*-butylpyridine (**3**), 6,6′-*tert*-butyl-2,2′-bipyridine (**4**),[2] and tarry material formed in some cases. Control over product distribution was accomplished by varying the molar ratio of *tert*-butyllithium to pyridine and the mode of addition. The use of excess *tert*-butyllithium also minimized the yields (max 8%) of monosubstitution product, 2-*tert*-butylpyridine (**5**). The results are summarized in Table I.

TABLE I

REACTION OF PYRIDINE WITH *tert*-BUTYLLITHIUM[a]

tert-BuLi/pyridine[g]	Overall yield, %	Yield, %[b] 1	2	3	4[c]	5
2.5[d]	69	30 (25)	20 (19)	10 (9)	1	8 (6)
5[d]	70	27 (17)	31 (31)	7	1	4 (3)
10[e]	72	6	54 (43)[f]	9	2	1
20[e]	90	5	55 (26)[f]	11	15	4

[a] Addition was carried out at −75° under dry nitrogen followed by 7-hr reflux at 100°. [b] Glpc yields, based on pyridine. Isolated yields are in parentheses. All compounds were isolated in >95% purity by fractional distillation, sublimation, and/or crystallization. [c] Approximately 0.5 g was isolated in pure form from the reaction residue. [d] See Experimental Section, procedure A; scale, 0.2 mol of pyridine. [e] See Experimental Section, procedure B; scale, 0.01 mol or 0.02 mol of pyridine. [f] Low isolated yield is due to small scale with unavoidable mechanical losses. [g] Molar ratio.

The crude product mixture was directly resolved into its components, each >95% pure, by one careful fractionation using a highly efficient distilling apparatus. In those trials in which >50% yield of **2** were realized, this solid could be crystallized out of the crude mixture upon cooling and subsequently purified by vacuum sublimation. This procedure thus constitutes the preferred method for obtaining **1** and **2**.

The identities of compounds **1** and **5** were established by comparison of boiling points, infrared and proton nmr spectra, and melting points of the chloroaurates

(1) See, for example, F. E. Condon, *J. Amer. Chem. Soc.*, **87**, 4494 (1965), and reference cited therein.

(2) H. C. Brown and B. Kanner, *ibid.*, **88**, 986 (1966); **75**, 3865 (1953).

(3) H. C. van der Plas and H. J. den Hertog, *Recl. Trav. Chim. Pays-Bas*, **81**, 841 (1962).

(4) A multistep synthesis (overall yield, 42%) of **2** *via* treatment of 2,4,6-tri-*tert*-butylpyrylium tetrafluoroborate with alcoholic ammonia has been reported: K. Dimroth and W. Mach, *Angew. Chem., Int. Ed. Engl.*, **7**, 460 (1968).